CLAIMS

We claim:

1. A targeting construct comprising:

(a) a first polynucleotide sequence homologous to a nuclear hormone receptor gene;

(b) a second polynucleotide sequence homologous to the nuclear hormone receptor gene; and

(c) a selectable marker.

2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.

3. A method of producing a targeting construct, the method comprising:

(a) providing a first polynucleotide sequence homologous to a nuclear hormone receptor gene;

(b) providing a second polynucleotide sequence homologous to the nuclear hormone receptor;

(c) providing a selectable marker; and

(d) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.

4. A method of producing a targeting construct, the method comprising:

(a) providing a polynucleotide comprising a first sequence homologous to a first region of a nuclear hormone receptor gene and a second sequence homologous to a second region of a nuclear hormone receptor gene;

(b) inserting a positive selection marker in between the first and second sequences to form the targeting construct.

5. A cell comprising a disruption in a nuclear hormone receptor gene.

6. The cell of claim 5, wherein the cell is a murine cell.

7. The cell of claim 6, wherein the murine cell is an embryonic stem cell.

8. A non-human transgenic animal comprising a disruption in a nuclear hormone receptor gene.

9. A cell derived from the non-human transgenic animal of claim 8.

10. A method of producing a transgenic mouse comprising a disruption in a nuclear hormone receptor gene, the method comprising:

(a) introducing the targeting construct of claim 1 into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse.

11. A method of identifying an agent that modulates the expression of a nuclear hormone receptor, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a nuclear hormone receptor gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the expression of nuclear hormone receptor in the non-human transgenic animal is modulated.

12. A method of identifying an agent that modulates the function of a nuclear hormone receptor, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a nuclear hormone receptor gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the function of the disrupted nuclear hormone receptor gene in the non-human transgenic animal is modulated.

13. A method of identifying an agent that modulates the expression of nuclear hormone receptor, the method comprising:

(a) providing a cell comprising a disruption in a nuclear hormone receptor gene;

(b) contacting the cell with an agent; and

(c) determining whether expression of the nuclear hormone receptor is modulated.

14. A method of identifying an agent that modulates the function of a nuclear hormone receptor gene, the method comprising:

(a) providing a cell comprising a disruption in a nuclear hormone receptor gene;

(b) contacting the cell with an agent; and

(c) determining whether the function of the nuclear hormone receptor gene is modulated.

15. The method of claim 13 or claim 14, wherein the cell is derived from the non-human transgenic animal of claim 8.

16. An agent identified by the method of claim 11, claim 12, claim 13, or claim 14.

17. A transgenic mouse comprising a disruption in a nuclear hormone receptor gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: a spleen abnormality, an abnormality of the thymus, or an abnormality in the lymph nodes.

18. The transgenic mouse of claim 17, wherein the spleen abnormality is reduced weight of the spleen relative to a wild-type mouse.

19. The transgenic mouse of claim 17, wherein the spleen abnormality is reduced size of the spleen relative to a wild-type mouse.

20. The transgenic mouse of claim 17, wherein the spleen abnormality is a reduced spleen to body weight ratio relative to a wild-type mouse

21. The transgenic mouse of claim 17, wherein the spleen comprises lymphoid depletion.

22. The transgenic mouse of claim 21, wherein the lymphoid depletion is found in the periarteriolar lymphoid sheaths.

23. The transgenic mouse of claim 17, wherein the abnormality of the thymus is reduced size of the thymus relative to a wild-type mouse.

24. The transgenic mouse of claim 17, wherein the abnormality of the thymus is reduced weight of the thymus relative to a wild-type mouse.

25. The transgenic mouse of claim 17, wherein the abnormality of the thymus is a reduced thymus to body weight ratio relative to a wild-type mouse.

26. The transgenic mouse of claim 17, wherein the thymus comprises lymphoid depletion.

27. The transgenic mouse of claim 17, wherein the abnormality of the thymus is consistent with thymic dysplasia.

28. The transgenic mouse of claim 17, wherein the abnormality of the thymus is consistent with atrophy of the thymus.

29. The transgenic mouse of claim 17, wherein the abnormality of the lymph nodes is lymphoid depletion.

30. A method of producing a transgenic mouse comprising a disruption in a nuclear hormone receptor gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: spleen abnormality, an abnormality of the thymus, or an abnormality in the lymph nodes, the method comprising:

(a) introducing a nuclear hormone receptor gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a nuclear hormone receptor gene.

31. A cell derived from the transgenic mouse of claim 17 or claim 30.

32. A method of identifying an agent that ameliorates a phenotype associated with a disruption in a nuclear hormone receptor gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a nuclear hormone receptor gene; and

(b) determining whether the agent ameliorates at least one of the following phenotypes: spleen abnormality, an abnormality of the thymus, or an abnormality in the lymph nodes.

33. A method of identifying an agent which modulates nuclear hormone receptor expression, the method comprising:

(a) administering an agent to the transgenic mouse comprising a disruption in a nuclear hormone receptor gene; and

(b) determining whether the agent modulates nuclear hormone receptor expression in the transgenic mouse, wherein the agent has an effect on at least one of the following behaviors: spleen abnormality, an abnormality of the thymus, or an abnormality in the lymph nodes.

34. A method of identifying an agent which modulates a behavior associated with a disruption in a nuclear hormone receptor gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a nuclear hormone receptor gene; and

(b) determining whether the agent modulates coordination and balance of the transgenic mouse.

35. A method of identifying an agent which modulates nuclear hormone receptor gene function, the method comprising:

(a) providing a cell comprising a disruption in a nuclear hormone receptor gene;

(b) contacting the cell with an agent; and

(c) determining whether the agent modulates nuclear hormone receptor gene function, wherein the agent modulates a phenotype associated with a disruption in a nuclear hormone receptor gene.

36. The method of claim 35, wherein the phenotype comprises at least one of the following: a spleen abnormality, an abnormality of the thymus, or an abnormality in the lymph nodes.

37. An agent identified by the method of claim 32, claim 33, claim 34, or claim 35.

38. A transgenic mouse comprising a disruption in a nuclear hormone receptor gene, wherein the transgenic mouse exhibits decreased coordination and balance relative to a wild-type mouse.